Lessons From an Older Biologic 'Reassuring'

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BIRMINGHAM, ENGLAND — Long-term follow-up of a cohort of patients with rheumatoid arthritis who were treated with a lymphocytotoxic monoclonal antibody during the early 1990s offers reassuring support for the safety of current lymphocyte-depleting agents such as rituximab, John D. Isaacs, M.D., said at the joint meeting of the British Society for Rheumatology and the German Society for Rheumatology.

The first humanized monoclonal antibody, alemtuzumab (Campath-1H), was given to 53 patients with severe rheumatoid arthritis (RA) in the United Kingdom between 1991 and 1994.

'Mortality also did not differ according to total dose of the monoclonal antibody or the number of courses received.'

Campath—so named because it was developed at the Cambridge University pathology laboratory—depleted both B and T cells, rendering patients profoundly lymphopenic, according to Dr. Isaacs.

This monoclonal antibody, alemtuzumab, recognizes CD52, which is present on the surface of many lymphocytes and on natural killer cells and macrophages.

"Our rationale for giving Campath to patients in the early 1990s, before [anti–tumor necrosis factor–α] therapy became available, was that it would deplete the autoreactive immune system and that when reconstitution occurred the immune system would be healthy," said Dr. Isaacs, professor of clinical rheumatology, School of Clinical Medical Sciences, University of Newcastle Upon Tyne (England).

The patients treated with Campath had severe, long-standing disease, with a median duration of 9 years. All had failed multiple disease-modifying drugs. Following one or more short courses of treatment with Campath, there was "dramatic" clinical improvement that in some cases was long lasting.

"But what we were not expecting was the lymphopenia, which ended up being quite prolonged," he said.

During the first year after treatment, the CD4 counts were very low, and they slowly rose during the subsequent 5 years, but the levels never returned to normal. B-cell depletion was not as persistent.

In an earlier follow-up report on this group, Dr. Isaacs and his colleagues noted that 73-84 months after treatment the median CD4 count was 185 cells/μL, the median CD8 count was 95 cells/μL, and the median B-cell count was 115 cells/μL (Arthritis Rheum. 2001;44:1998-2008). This represents severe immunosuppression; the Centers for Disease Control and Prevention considers a CD4 count lower than 200 cells/μL in an HIV-positive patient a signal of AIDS.

These patients have now been followed for a mean of 12 years in a retrospective case-control study, in which outcomes for each patient were compared with two matched controls from the European League Against Rheumatism database of patients who received conventional immunosuppressive therapies such as azathioprine and cyclophosphamide.

Total follow-up is now roughly 464 patient-years.

There has been no significant difference in mortality between the two groups, with 20 deaths among the Campath cases and 37 among the controls.

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"The causes of death were primarily the complications we now associate with RA itself—vascular events and infections—and with the notable exception of one case of non-Hodgkin's lymphoma there were no infections or malignancies that one would normally associate with immunosuppression," Dr. Isaacs said.

Despite the availability of successful therapies such as the TNF-α blockers and the fact that Campath is little used today, there still is a need for lymphocyte-depleting agents, he said.

"In fact, some of us believe that therapeutic tolerance in autoimmune disease will only become possible against a background of lymphocyte depletion," he added. ■